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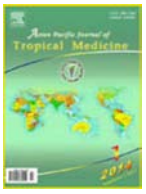

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A review study on analgesic applications of Iranian medicinal plants

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ABSTRACT

Numerous side effects of synthetic drugs have caused medicinal plants to be regarded in recent decades as a reliable source of new drugs. Regarding the analgesic effects of many plants that are pointed in traditional medicine of Iran, many studies have been performed in this field that have caused need to be reviewed. In this study, different methods of testing pain, analgesic activity and possible compounds of medicinal plants and also the possible mechanisms actions of these plants are presented. The data presented in this review paper provide scientific information that might be used for isolation of potentially active compounds from some of these medicinal plants in future.

1. Introduction

Based on definition of international association of pain study, pain is an undesirable mental and emotional experience that is associated with possible or actual damage of tissue or is created in some periods of these types of pains. Pain is created by different reasons such as harmful heat, stretch, electrical flow, necrosis, inflammation, laceration and spasm[1]. Pain is also caused by a wide variety of diseases, surgical interventions and trauma. Degenerative diseases like rheumatoid arthritis, polymyalgia rheumatica, as well as heart, asthma, cancer and inflammatory bowel diseases are also associated with inflammatory processes and pain. It is a complex experience in which cognitive, affective and behavioral features, representing psychological conditions are affected[2]. In most cases, pain is secondary to other complications such as diabetic nephropathy[3-6].

More than 50 million American populations due to involving in pain conditions are partially or totally disabled. The United States Center for Healthcare Statics carried out an eight-year study, demonstrating 32.8% U.S. populations were suffering from chronic pain[7].

Recent studies have shown that 22% of primary care patients suffered from pain which persists for more than six months and in some cases the percentage rises to 50% which is related to significant impairment of social functioning and quality of life[8].

Although pain mainly is considered as a defense mechanism which is created when a tissue is damaged and caused a person show reaction and remove pain stimulant[4], however, in sever condition it impairs social functioning and reduces quality of life[1].

Millions of people suffering from different types of damage who wish to find a drug with more effect and less side effects in order to release themselves from the pain[9]. Medicinal plants have been suggested to presence natural effective substances for prevention or treatment of pain related conditions. Drugs with herbal origin have attracted attention of researchers and people by having low or no side effects[10,11]. These medicinal plants mostly possess

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antioxidant activities[3,12-16], and other than pain and inflammation, are effective on a lot of hard curable diseases such as diabetes and cancer which may increase free radicals and result in pain[6,17-20].

This paper was aimed to present Iranian medicinal plants which are used and shown promising results for prevention and treatment of pain and inflammation. The paper not only presents different kinds of pain, mediators of pain and inflammation but also discusses the pathophysiology of pain.

2. Acute and chronic pain

Pain is divided into two main types: rapid or fast and slow pain. Rapid pain is felt one second or more after stimulant strike and then its severity is increased slowly during several seconds or even minutes[20]. Fast pain is described by some names like electrical, acute, tingling, and stabbing pain. Slow pain also has different names including unclear, chronic, throbbing and burning pain. This type of pain is accompanied by tissue destruction and can lead to unbearable pain. This pain almost can be created in both skin and tissue or deep organism[2]. Fast pain mainly is created by mechanical or heat painful stimuli while slow and chronic pain is more stimulated by painful chemical stimulants[1]. Pain is described as one of the five critical signs that many negative outcomes are created if it is not regarded[2].

3. Pain mediators

High ratio of somatic or visceral pain receptors can be stimulated or sensitized by different stimulants and inflammatory mediators like bradykinin, prostaglandins, leukotrienes, serotonin, histamine, capsaicin and free radicals[21-23]. The following cases can be mentioned on pain mediators.

3.1. Glutamate

Amino acid stimulated by glutamate can perform through ion channels dependent to ligand (glutamate ionotropic receptors) or glutamate metabotropic receptor (mGLuRs) coupled with G protein[24]. Glutamic acid and gamma amino butyric acid (GABA) is respectively two main nervous excitatory and inhibitory transferor of central nervous system in mature mammals. These transferors perform through two metabotropic and ionotropic receptors. Ionoteropic receptors are ligand-gated ion channels that are involved in rapid synaptic transfer while metabotropic receptors belong to big family of G receptors of protein (GPCRs) and committed to control GABA and glutamate. Metabotropic glutamate receptors and metabotropic GABA receptors have play in different levels of pain that control pain transfer[25]. Recently it has been determined that glutamate interferes in transferring sensory input especially during pain transferring[26].

3.2. Substance P

Secretion of substance P through axon distributions in skin causes vasodilation, blood capillaries dilation and release of histamine from mast cells. Sensitivity of pain receptors surrounding surgery place causes secondary through substance P and causes secondary hyperalgesia[27]. Substance P is available inside some primary sensatory neurons that terminate to surface area of dorsal horn of spinal cord. Intensive stimulation of primary afferent fibers distributions that activate A-delta and C-delta fibers, cause secretion of substance P[28].

3.3. Serotonin

Many neurons in raphe nuclei secrete serotonin as a neurotransmitter. Serotonin can inhibit pain neurons and possibly plays an important role in endogenous anti-pain system. Other neurons of brainstem release epinephrine and norepinephrine in spinal cord. These neurons also inhibit pain neurons[29].

3.4. Histamine

Histamine has main role in allergic inflammation. Inflammatory responses resulted by histamine release are long and performed by mediator of histamine receptor H1. Antagonists of H1 receptors are usually recognized as antihistamines and have been used to treat allergy for many years. Discovery of histamine four receptor and its expression in different inflammatory cells make it possible to reevaluate histamine functions[30].

3.5. Nervous growth factor (NGF)

This factor possibly interferes in inflammatory pain directly or indirectly. Inflammatory mediators like cytokines, increase production of NGF in inflamed tissues[31]. NGF stimulates mast cells in releasing of histamine and serotonin. Also this factor can stimulate thermal hyper allergy directly through performing on peripheral terminals of primary afferent fibers[32]. NGF is a member of neurotrophin family and is determinant of survival of pain neurons. Recently

important role in pain performance has been shown for it in adults. This factor in skin causes thermal hyper-allergy during a few minutes. Mast cells are important components in action of NGF[33].

3.6. Adenosine and adenosine phosphate

Inflammation and tissue damage possibly release adenosine and adenosine phosphate [adenosine monophosphate, adenosine diphosphate, adenosine triphosphate (ATP)] and secret into extracellular space and activate pain receptors[33]. ATP receptors are found in primary sensory nerves of dorsal root ganglion and in peripheral nerves. ATP possibly activates pain neurons in healthy skin through P2X2-P2X3 receptors and purinergic P2X3 receptors[34].

3.7. Indigenous cannabinoids

Indigenous cannabinoids are a family of bioactive lipids that activate cannabinoid receptors to regulate nervous transfer. They are available in brain in low amounts and participate in regulating different brain functions including pain perception, appetite and memory. They are produced in level of postsynaptic terminals that need calcium ion penetration and spread in surface of presynaptic cannabinoid receptors[35]. Irritant stimulant increases indigenous cannabinoid spread. This action expresses their role in regulation of pain[36]. Endocannabinoids decrease pain. Natural and artificial cannabinoids have ability to decrease pain feeling, inflammation, inflammatory pain, hyper allergy and prevent secondary tissue damage in traumatic wounds[37].

4. Analgesics

Although a wide variety of different drugs from various groups have analgesic activities, opioids and nonsteroidal anti-inflammatory drugs are the two main groups of drugs which are used to combat pain.

4.1. Opioids

Opioids perform their effects through binding to special types of opioid receptors which exist throughout the brain and spinal cord[38,39]. Morphine is the first natural opioid and its effects were determined. Further research in mammals led to identification of opioids with internal origin and also receptors of these opioids. Encephalin and endorphins, especially beta endorphin, are of endogenous opioids. Repeated administration of them results in three states: tolerance, physical and mental dependence.

Tolerance is occurred after repeated use of opioid drugs and the person needs to keep increasing the amount used to achieve that first effect. Consumed opioids, like morphine, affect on opioid receptors (δ, κ, μ) with internal origin and decrease peptides with internal origin by a negative feedback[40]. Morphine has been used for many centuries, but is not free of side effects. Respiratory problems, napping, decrease in gastrointestinal mobility, nausea, and changes in automatic nervous system and endocrine secretion are some of the morphine side effects[41].

4.2. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are used extensively to control chronic pain. These drugs inhibit cyclooxigenase enzyme and have three important properties: decreasing inflammation, pain and fever. Depending on the drug, this group has renal, digestive and even cardiovascular effects[2].

4.3. Topiramate

Topiramate has been approved by Food and Drug Administration in America as anti-migraine drug. Topiramate has been revealed to increases activity of GABA receptors by inhibiting voltage-dependent calcium and sodium channels and inhibits glutamate metabotropic receptors[2].

5. Methods of testing pain in animals

5.1. Hot plate test

In this method, mice are individually put on plate 3-4 times in 3-5 min intervals to decrease nervous pressure. The time duration between placing mice on plate and licking time is considered as threshold and delay of licking or kicking time by animal in different times is recorded. To calculate more exactly, each mouse is put on plate for 4-5 times in 5 min intervals and the average is obtained. Cut off time to avoid tissue damage is considered for animal[42]. Pain control mechanisms are introduced in this test[32]. Hot plate test is a selective test for opioid-like compounds[33]. This test is an extra-spinal pain model. The main property of this test is able to provide automatic defensive behaviors[43].

5.2. Writhing test

In this test, acetic acid solution is injected to mice,

intraperitoneally. Then the number of writhing is recorded for 30 min after injection of acetic acid[39]. Provided writhings include contractions of abdominal muscles followed by opening back feet or stretching all body in animal[44]. Contractions of abdominal muscles depend on sensitivity of pain receptors to compounds like prostaglandins.

Tissue damage causes release of compounds like prostaglandins, bradykinin, serotonin, substance P, histamine and PGF2α and causes expression of inflammatory pain by induction of capillary permeability. Analgesic activity of opioid agonists and non-steroidal anti-inflammatory drugs can be determined by this test. In addition to prostaglandins, several inflammatory mediators including tumor-necrosis-factor-α and interleukins are also contributed to nociceptive response to acetic acid. Also response of this test depends on macrophages activity and peritoneal mast cells. Macrophages stimulate arachidonic acid release and formation of F2 or E2 prostaglandins by secretion of bradykinin. Mast cells synthesize inflammatory mediators including interleukins, placket activating factor, granulocyte-macrophage stimulating factor, macrophage inflammatory protein and arachidonate metabolites, prostaglandins and leukotrienes[34].

5.3. Light tail flick test

In the light tail flick, the mouse is placed in restrainer device in a way that animal tail is outside chamber. In this method, the lamp light is used to create pain. Light beam is focused on tail and after a while, the animal flicks its tail in result of pain created by heat. At first, animal tolerance is measured and the tolerance time is considered as control latency. Then, in different intervals, up to 120 min after drug administration, the pain tolerance time duration is recorded again and maximum analgesic response is calculated by the below formula:

$$\text{Maximum analgesic response}=\frac{\text{Test latency}-\text{Control latency}}{\text{Cut off time}-\text{Control latency}}\times 100$$

Cut off time is the maximum tolerance time to prevent animal tail damage[40].

5.4. Tail immersion

Hot water tail immersion test or briefly tail immersion is used to study acute pain. First, mouse is put into restrainer and after 20 min, mouse's tail is immersed into the hot water bath. Time duration of placing tail in water until mouse withdraws its tail from water is considered as acute pain threshold. Tail of each mouse is placed in water 5 times in 7 min intervals and mean threshold of these times is calculated for each mouse. After calculating mean threshold in each mouse, the percent of analgesia index is calculated according to below formula[44]:

$$\text{Analgesia index}=\frac{\text{Drug latency}-\text{Control latency}}{\text{Cut off time}-\text{Control latency}}\times 100$$

5.5. Formalin test

In this method, a glass container is used to placing animal in it and observing animal responses. A mirror is positioned underneath the container and is set at a 45° angle to secure a clear vision. To perform test, 20 μL of 2.5% formalin is injected subcutaneously into the surface of the paw. Then time durations of licking/biting of the formalin-injected paw is recorded during two delay and rapid stages. Usually early 0-5 min is called acute phase and late 5-60 min is called chronic phase[45].

6. Effects of medicinal plants extracts on pain

Due to potential side effects and low efficacy of synthetic and chemical drugs, consumption of other complementary drugs especially herbal remedies to control pain is increasing[11]. Effects of herbal extracts have been studied by different pain tests including writhing test, light tail flick test, tail immersion, hot plate test and formalin tests.

Different extracting methods have also been used in order to produce extracts that the most frequently methods are percolation, Soxhlet and maceration[46-48]. The extracts are often aqueous, ethanolic, hexane, ethyl acetate and aqueous-ethanolic types[49-53]. Some of the are plants presented in Table 1, such as *Saliva hydrangea, Thymus vulgaris, Melissa officinalis, Menthe pulegium, Ziziphora tenuior*, *Stachys lavandulifolia*, *Gundelia tournefortii* L., *Datura stramonium* L., *Solenanthus circinnatus*, *Carum copticum*, *Apium graveolens*, *Allium jesdanum*, *Pistacia vera* L., *Vitex agnus*, *Sambucus ebulus*, *Portulaca oleracea*, *Piper nigurm*, *Juglans regia*, *Melilotus officinalis*, *Matricaria chamomilla*, *Artemisia herba*, *Crocus sativus*, *Foeniculum vulgare*, *Colchicum szovitsii*, and *Elaeagnus angustifolia* which have analgesic effects in traditional medicine. Among plants which their analgesic effects have been proved, the most effective species belongs to Lamiaceae family. Plants affecting pain, in addition to analgesic properties, have different therapeutic properties. For example, ability to treat rheumatism, gout, migraine, relax muscle, wound healing, antispasmodic[54-56], anti-inflammation, edema, anti-blood pressure[57,58], antioxidant, anti-hormonal[59,60], antiviral[61], antimicrobial[62], preventing Alzheimer, reinforcing memory[63], anti-diabetes[64,65], renal,

Table 1

Some important medicinal plants with antinociceptive activity.

Family name	Scientific name	Pain test type	Fractions and used organism	Possible mechanism	Reference
Lamiaceae [Labiatea]	*Saliva hydrangea*	Light tail flick	Essence and hydroalcoholic extract of leave and flower	Inhibiting synthesis path of prostaglandins	73
	Lavandula officinalis	Tail flick and formalin test	Methanolic	Effect on inflammatory processes	74,75
	Thymus vulgaris	Tail flick hot plate	Plant hydroalcoholic	–	76
	Melissa officinalis	Tail flick	Aqueous extract of branches	Central anti-pain mechanism	77
	Menthe pulegium	Formalin test	Aqueous-alcoholic extract of leave	Inhibiting NO synthesis, inflammatory mediators and NMDA receptors and irritating opioid receptors	78
	Teucrium hyrcanicum	Formalin, tail flick and writhining	Aqueous extract of leave	Inhibiting prostaglandins synthesis and central nervous system	79
	Salvia hypoleuca	Formalin test	Alcoholic extract of leave	Opioid system and inhibiting pre-inflammatory mediators	80
	Ziziphora tenuior	Writhing test	Aqueous-alcoholic extract of leave and branches	Inhibiting release of acid arachidonic and synthesis of prostaglandins and effect on opioid system	81
	Teucrium polium	Tail flick test	Aqueous	Binding to pain receptors, affecting ligand-sensitive channels and decreasing sodium entrance	82
	Origanum vulgare L.	Tail flick test	Aqueous	Antioxidant compounds, inflammatory processes and opioid receptors	83
	Satureja hortensis Linn.	Formalin, tail flick test	Aqueous extract of seed	Through central mechanisms and inflammatory processes	84
	Salvia sclarea	Formalin, tail flick and writhing test	Alcoholic extract of aerial and hydroalcoholic parts of leave	Peripheral effects and inflammatory processes and opioid receptors	85
	Mentha piperita Linn.	Formalin, hot plate and writhing test	Alcoholic extract of leave	Peripheral and central effects	45
	Stachys lavandulifolia	Formalin and tail immersion test	Hydroalcoholic extract of branches	Inhibiting cyclooxigenase	86
Asteraceae	*Artemisia dracunculus*	Formalin test	Leave powder (edible prescription)	Presence of flavonoids and some substances with benzodiazepines property	87
	Matricaria chamomilla	Formalin test	Chamamill	Cholinergic mechanisms	88
	Gundelia tournefortii L.	Formalin test	Aqueous-alcoholic extract of aerial branches	Serotonergic, GABAergic and adrenergic and inflammatory processes	89
	Tanacetum parthenium	Hot plate	Alcoholic extract of aerial organisms	Inflammatory processes	89
Solanaceae	*Solanum melongena*	Formalin test	Hydroalcoholic extract of fruit	Peripheral anti-pain mechanisms and cholinergic paths	90
	Hyoscyamus niger	Tail immersion	Alcoholic extract of seed	Opioid and cholinergic mechanisms	91
	Datura stramonium L.	Formalin and hot plate test	Alcoholic extract of seed	Reinforcing opioid system and decreasing peripheral and central hyperalgesia mediators	92
Boraginaceae	*Solenanthus circinnatus*	Formalin and tail flick	Hydroalcoholic extract of root	Through inhibiting central and peripheral paths	93
Euphorbiaceae	*Euphorbia helioscopia*	Writhing test	Alcoholic extract of aerial sections	Effect of flavonoids and steroids	46
Umbelliferae	*Carum copticum*	Formalin	Aqueous and oil extract of fruit	Effect of essential fatty acids	94
	Dorema aucheri	Formalin	Aqueous-alcoholic extract of aerial parts	Inhibiting NO synthesis and NMDA receptors and irritation of opioid and adrenergic system	95
	Petroselinum crispum L.	Formalin and acid acetic test	Alcoholic extract of leave	Activating anti-pain paths	96
	Apium graveolens	Formalin	Hydroalcoholic extract of fruit	Inhibition of cyclooxigenase	97
Lilaceae	*Allium jesdanum*	Hot plate and tail flick	Aqueous- alcoholic extract of leave	Central anti-pain properties and affecting on opioid receptors	98
Anacardiaceae	*Pistacia vera* L.	Hot plate, writhing and formalin test	Hydroalcoholic extract of resin	Inhibiting opioid receptors and inflammatory mediators	99
Adoxaceae	*Sambucus ebulus*	Writhing and hot plate	Hexane, ethyl estate and methanolic extract of fruit, leave and root	Inhibition of prostaglandins synthesis	98
Verbenaceae	*Vitex agnus castus*	formalin test	Hydroalcoholic extract of fruit	Inhibition of prostaglandins synthesis and other inflammatory mediators	100
Apiaceae	*Coriandrium sativum*	formalin test	Aqueous extract of seed	–	101
Fabaceae	*Trigonella foenum-graecum*	formalin test	Aqueous extract of leave	Effect of serotonergic system	102
Portulacaceae	*Portulaca oleracea*	Hot plate and tail flick	Aqueous- alcoholic extract of aerial sections	Central and peripheral effects	103
Palmaceae	*Phoenix dactylifera*	Formalin, tail flick and paw pressure	Aqueous extract of fruit	Increase of blood carbohydrates and β-endorphins level and peripheral mechanisms	104
Lauraceae	*Cinnamomum zeylanicum*	Formalin	Aqueous-alcoholic extract of stem skin	Inhibiting NO synthesis and COX2 and inhibition of prostaglandins production and irritation of opioid receptors	70
Artemisia	*Artemisia siberi* Besser.	Formalin	Aqueous-alcoholic extract of branches	Inhibiting calcium release, blocking TRPAI receptors, inhibiting NO synthesis and cytokines and prostaglandin E2	104
	Artemisia herba-alba	Formalin, tail flick	Aqueous-alcoholic extract of stem and leave	Irritation of GABA A receptors	105
Cannabaceae	*Humulus lupulus* L.	Formalin	Aqueous extract of plant	Opioid receptors	106
Apiaceae	*Foeniculum vulgare*	Formalin	Aqueous extract of fruit	Serotonergic and hystaminergic receptors	79
Iridaceae	*Crocus sativus*	Formalin	Aqueous extract of flower	Possible inhibition of NMDA receptors and nitric oxide synthesis	107
Zingiberaceae	*Zingiber oficinalis*, Z.o	Formalin	Alcoholic extract of rhizome	Inhibiting release of peripheral mediators, cytokine, TNF and interleukin-1β, nuclear factor kappa B	108
	Cuminum cyminum L.	Formalin	Aqueous extract of fruit	–	2
Elaeagnacea	*Elaeagnus angustifolia*	Formalin and writhing test	Aqueous extract of fruit and leave	Inhibiting pre-inflammatory mediators and NMDA receptors	109
Droseraceae	*Drosera spatulata*	Formaline	Aqueous extract of plant	Activity of paragigantocellularis cell	110
Fabaceae	*Glycyrrhiza glabra*	Formaline and tail flick test	Hydroalcoholic extract of root	Inhibiting immigration of white globules and production of inflammatory meditators and Neutrophils	111
Hypericaceae	*Hypericum perforatum*	Formaline and tail flick test	Aqueous extract of flowering branches	Inhibiting COX1 and 5-LO enzyme	65
Piperaceae	*Piper nigurm*	Formaline test	Methanolic extract of fruit	Central and anti-inflammatory	112
Juglandaceae	*Juglans regia*	Formaline test	Alcoholic extract of leave	Inhibiting COX1 enzyme, calcium release inhibiting and cholinergic, histamine and adrenergic mechanisms	113
Rosaceae	*Rosa demascena*	Hot plate and tail flick test	Alcoholic, aqueous and chloroform extract of flower	Opioid system	114
Papaveraceae	*Glaucium grandiflorum*	Formaline and hot plate	Methanolic extract of aerial parts	Alkaloids	115
Comositeae	*Matricaria chamomilla*	Formaline and hot plate	Methanolic extract of flower	Inflammatory processes	116
	Lactuca sativa longifolia	Formaline and tail flick test	Aqueous-alcoholic extract of leave	Central and peripheral mechanisms	117
Papilionaceae	*Securigera securidaca* L.	Formaline test	Hydraualcoholic extract of seed	Inhibiting NO and COX2 synthesis	118
Leguminosae	*Melilotus officinalis*	Formaline and tail flick test	Methanolic extract of fruit	Opioid system	119
Berberidaceae	*Berberis vulgaris* L.	Formaline test	Aqueous-alcoholic extract of root	Opioid system	120

NMDA: N-methyl-D-aspartate.

digestive and respiratory effects[66-68], increasing secretive activity and digestive movement[69,70], anti-anxiety, and abortifacient effects[71,72]. Their compounds affecting on pain include flavonoids (quercetin), volatile oils (monoterpenes and sesquiterpenes), phenolic compounds like thymol and carvacrol, coumarin, glycoside steroids, alkaloid compounds like Atropine, scopolamine and hyoscine, organic acids like caffeic acid, rosmarinic acid, nicotinic acid, as well as phenolics, GABA, tannins, essential oils, pinene, limonene and cineol, monoterpenes, alcohols, diterpenoids, riboflavin, terpenes, resins, iridoids, saponins, cineol, myrcene, α-thujene and camphor.

7. Discussion

Pain is a response including emotional, sensory and mental sections. Disease, inflammation and damage to peripheral and central nervous system cause clear changes in pain paths like change in gene expression and increase in production of molecules like neurotransmitters, enzymes and receptors. Suffering from pain in long term imposes undesirable mental effects. So, human has been always seeking to a solution to decrease or eliminate pain[59]. Pain is a phenomenon considered as a warning factor but it is an undesirable feeling and human has tried to resist it. Analysis of researches made in recent decades demonstrates special attention paid to analgesic drugs, since analgesic drugs available in medicinal market show an extensive range of undesirable side effects[110].

Flavonoids are natural polyphenol compounds available in plants that have analgesic and anti-inflammation properties[118]. Flavonoids can pass through brain-blood barrier and control pain by different mechanisms like affecting GABA A, opioid, a-adrenergic receptors and inhibiting enzymes involved in inflammation in brain. Presence of GABA A, opioid, and adrenergic receptors is reported in different areas of nervous system including in rostral ventrolateral medulla that paragigantocellular nucleus is a part of it. Irritation of these receptors causes pain relief[121,122]. Flavonoids, by inhibiting cyclooxigenase in tissues, prevent formation of prostaglandins. Prostaglandins cause stimulation of pain receptors.

Plants containing flavonoids perform many of their effects by inhibiting the cyclooxigenase enzyme[44]. Flavonoids are considered as the inhibitors of synthesizing enzyme nitric oxide and prevent NO production that is increased following formalin injection, so its decrease leads to analgesic activity. Other studies show that flavonoids, by inhibiting activity of NMDA receptors, decrease intracellular calcium and in following activity of synthesizing enzyme, nitric oxide and calcium-dependent phospholipase A2 is decreased and in result by decreasing NO and prostaglandins show their analgesic effects. Inhibiting phospholipase A2 enzyme activity inhibits transformation of phosphatidic acid to arachidonic acid and in result synthesis of prostaglandins is inhibited[123]. Regarding available evidence, flavonoids inhibit production of prostaglandin [E] from *arachidonic* acid in response to inflammatory stimulants by inhibiting TNF and inhibiting cyclooxigenase enzyme[118,124].

Flavonoids including apigenin decrease accumulation of floating lipids that are necessary to signal pain so they reduce inflammatory pain by inhibiting accumulation of receptors and hormonal cascade[97]. Flavonoids available in *Artemisia dracunculus* decrease pain by protective property against oxidative stress resulted from hyperglycemic state and substances with property similar to benzodiazepines[119]. Direct effect of flavonoids on prostaglandins synthesis has been proved. Since NO is hyperalgesia mediator, so its decrease leads to analgesic activity. Flavonoids interfere in pain regulation through opioid system and adrenergic system. Among essential oils the compound alpha-eudesmol is inhibitor of omega-toxin-sensitive P/Q type calcium channels sensitive to omega toxin so can inhibit release of neurotransmitters from terminals of pain fibers in posterior horn of the spinal cord and finally decreases pain[111]. Glycyrrhizin is one of the compounds available in *Glycyrrhiza glabra* that applies its anti-inflammation effect by inhibiting immigration of white globules toward inflamed areas and inhibiting production of inflammatory mediators in neutrophils. Edible use of *Glycyrrhiza glabra* causes inhabitation of 11-β dehydrogenase enzyme and in following increase in level of blood cortisol. Possibly this substance decreases pain in the second phase of formalin test through decreasing inflammation[111].

Tannin, menthol and menthone are analgesic compounds in plants. Studies show that menthol has specific receptors in the cell membrane that leads to decrease in intracellular current in the rest state and increases pain threshold of cells. This compound decreases inward calcium current, irritability and amount of synaptic transfer by affecting calcium channels available in nervous cells membrane especially pain path neurons and leads to decreased pain perception. Regarding effect of menthol on kappa opioid receptors, possibly menthol available in plants extracts affect on these receptors and so inhibits current and transfer of pain signal and leads to decrease in pain perception[78]. Extract of some plants like *Portulaca* or parsley possibly apply their effects by activating systems interfering in analgesic paths like opioidergic, GABAergic, cholinergic and glutamatergic systems[103].

Inhibiting metabolism of arachidonic acid and nitric

oxide syntheses enzyme has been suggested for terpene compounds. Also linalool is one of the monoterpene compounds in cinnamon that affect on pain receptors and causes analgesia.

Linalool creates inhibitory capability in central nervous system neurons by opening potassium channels. Phenols like eugenol inhibit calcium entrance inside cell and so control release of neurotransmitters interfering in pain from terminals of afferent fibers in posterior horn of the spinal cord[90]. Phenolic monoterpenes like thymol and carvacrol have inhibitory effects on prostaglandins[125]. Gingerol substance as effective constituent of rhizome of ginger has ability to inhibit production of prostaglandins, leukotrienes and kinin as the most important inflammatory mediators. Moreover, it causes inhabitation of release of cytokines types, TNF and interleukin-1B and decrease of kappa factor by this extract. Ginger extract decreases production of NO and prostaglandin E2. These compounds are important mediators of vascular permeability increase. Decrease of vascular permeability and production of pain and inflammation mediators is considered as the most important inflammation reducing factors and consequently pain by ginger[108].

Alcoholic compounds like camphor causes decrease in inflammatory pain. Camphor prevents transient receptor potential V1 cation channels (also known as the capsaicin receptors), to be sensitized, so it has anti-pain effects. Camphor inhibits synthesis of NO, cytokines and prostaglandins E2. Also it causes inhibition of calcium release. Phenolic compounds like thymol imitate parasympathetic effects[126].

Aqueous extract of *Hypericum perforatum* causes analgesia through serotonergic, α-2 adrenergic and opioidergic mechanisms by inhibiting COX1 enzyme. It has been observed that sensory fibers are sensitized after release leukotrienes from damaged fibers. This sensitization is provided through B4 and D4 leukotrienes that are of metabolites of lipoxygenase. Lipoxygenase inhibitors prevent production of B4 and D4 leukotrienes. On the other hand, release of prostaglandins and D4 leukotriene and COX1 inhibitors decrease tonic pain created like second phase pain of formalin test and pain resulted from acetic acid. Lipooxigenase inhibitory role on release of prostaglandins and production of different B4 and D4 leukotrienes during the second phase has been made clear to a large extent[127]. The most important compounds of *Piper nigurm* fruit are p-perrine and p-pyridine alkaloids. P-pyridine compound affects directly on opioid receptors[112]. Analgesic effect of *Ziziphora tenuior* L. plant, belonging to Lamiaceae family, is attributed to pulegone that seems perform through inhibiting arachidonic acid and synthesis of prostaglandins and influencing opioids[117]. Lactucarium available in lettuce inhibits activity of enkephalinase enzyme and applies analgesic effect by maintaining encephalin[117].

It seems that terpenoids, flavonoids and alkaloids impose analgesic effects through inhibiting prostaglandins synthesis and central nervous system. Also terpenes, essential and volatile oils have analgesic effect[75].

8. Conclusion

There are various kinds of mediators such as prostaglandins, cytokines, histamine, serotonin, substace P, capsaicin, and nitric oxide which cause pain and inflammation. Pain is created by different reasons such as harmful heat, stretch, electrical flow, necrosis, inflammation, laceration and spasm[6]. Pain is also caused by a wide variety of diseases, surgical interventions and trauma. Degenerative diseases like rheumatoid arthritis, polymyalgia rheumatica, as well as heart, asthma, cancer and inflammatory bowel diseases are also associated with inflammatory processes and pain. Medicinal plants have been suggested to presence reliable remedies for prevention and treatment of pain related conditions. Traditional medicine in Iran can be used for pain-related ailments. The data presented in this review paper provides scientific information that might be used for isolation of potentially active compounds from some of these medicinal plants in future.

Conflict of interest statement

We declare that we have no conflict of interest.

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